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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Keiya Ozawa et al.	Art Unit:	1634
Serial No.:	09/905,591	Examiner:	Bradley L. Sisson
Filed:	July 13, 2001	Customer No.:	21559
Title:	GENE THAT IMPARTS SELECTIVE PROLIFERATIVE ACTIVITY		

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REQUEST FOR CONTINUED EXAMINATION UNDER 37 C.F.R. § 1.114

Applicants hereby request continued examination of the above-captioned application under 37 C.F.R. § 1.114. The application is a non-provisional application that was filed on or after June 8, 1995.

This request is being submitted after the filing of a Notice of Appeal and thus is to be considered as a request to withdraw the appeal and to reopen prosecution. Please enter the Reply to Final Office Action mailed in this case on December 21, 2004 (a courtesy copy of which is enclosed). Also enclosed are a Supplemental Information Disclosure

Statement, a Form PTO-1449 with a cited reference, and a Communication Regarding Information Disclosure Statements.

Enclosed is a check for $395.00 in payment of the fee required by 37 C.F.R. § 1.17(e) for this Request for Continued Examination. Applicants submit that no extension fee is due because this Request for Continued Examination is being submitted within two months of the date (December 27, 2004) the Office received Applicants' Notice of Appeal (as February 27, 2005 was a Sunday). However, if there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 28 February 2005

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PATENT
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Certificate of Mailing: Date of Deposit: December 21, 2004

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REPLY TO FINAL OFFICE ACTION

In reply to the Final Office Action that was mailed in connection with the above-captioned patent application on July 21, 2004, Applicants submit the following Amendments and Remarks.

Kindly amend the application as follows.

AMENDMENTS TO THE SPECIFICATION:

Amend the paragraph beginning at page 2, line 23, as follows.

The present invention seeks to overcome the problem of poor gene introduction efficiency by selectively amplifying *in vivo* or *ex vivo* hematopoietic stem cells into which a gene for treatment has been introduced. ~~The~~ An objective of the invention is to provide a fundamental technique for gene therapy targeting hematopoietic stem cells, and such.

AMENDMENTS TO THE CLAIMS:

Claims 1-6 (Canceled).

Claim 7 (Previously Amended): A method for causing selective proliferation of a cell, said method comprising

(a) providing a cell including a chimeric protein comprising a first polypeptide and a second polypeptide, wherein said first polypeptide comprises a ligand binding domain of a steroid hormone receptor that, upon ligand binding, self-associates, and wherein said second polypeptide comprises a cytokine receptor or a part thereof that, upon said self-association of said first polypeptide, imparts proliferation activity to said cell; and

(b) exposing said cell to a ligand capable of binding to said ligand binding domain of said first polypeptide of said chimeric protein, thereby causing selective proliferation of said cell.

Claims 8-17 (Canceled).

Claim 18 (Previously Presented): The method of claim 7, wherein said steroid hormone receptor is an estrogen receptor.

Claim 19 (Previously Presented): The method of claim 7, wherein said second polypeptide comprising a cytokine receptor or a part thereof that imparts proliferation activity to said cell is derived from a G-CSF receptor.

Claim 20 (Previously Presented): The method of claim 7, wherein said cell is a blood cell.

Claims 21-33 (Canceled).

Claim 34 (New): A method for causing selective proliferation of a cell, said method comprising

(a) providing a cell comprising

(i) a desired exogenous gene; and

(ii) a gene encoding a chimeric protein comprising a first polypeptide and a second polypeptide, wherein said first polypeptide comprises a ligand binding domain of a steroid hormone receptor that, upon ligand binding, self-associates, and wherein said second polypeptide comprises a cytokine receptor or a part thereof that, upon said self-association of said first polypeptide, imparts proliferation activity to said cell; and

(b) exposing said cell to a ligand capable of binding to said ligand binding

domain of said first polypeptide of said chimeric protein, thereby causing selective proliferation of said cell.

Claim 35 (New): The method of claim 34, wherein said steroid hormone receptor is an estrogen receptor.

Claim 36 (New): The method of claim 34, wherein said second polypeptide comprising a cytokine receptor or a part thereof that imparts proliferation activity to said cell is derived from a G-CSF receptor.

Claim 37 (New): The method of claim 34, wherein said desired exogenous gene and said gene encoding a chimeric protein are located on the same molecule.

Claim 38 (New): The method of claim 34, wherein said desired exogenous gene and said gene encoding a chimeric protein are located on separate molecules.

Claim 39 (New): The method of claim 34, wherein said cell is a blood cell.

Claim 40 (New): A method for causing selective proliferation of a cell, said method comprising

(a) providing a cell including a vector that expresses a chimeric protein comprising a first polypeptide and a second polypeptide, wherein said first polypeptide comprises a ligand binding domain of a steroid hormone receptor that, upon ligand binding, self-associates, and wherein said second polypeptide comprises a cytokine receptor or a part thereof that, upon said self-association of said first polypeptide, imparts proliferation activity to said cell; and

(b) exposing said cell to a ligand capable of binding to said ligand binding domain of said first polypeptide of said chimeric protein, thereby causing selective proliferation of said cell.

Claim 41 (New): The method of claim 40, wherein said steroid hormone receptor is an estrogen receptor.

Claim 42 (New): The method of claim 40, wherein said second polypeptide comprising a cytokine receptor or a part thereof that imparts proliferation activity to said cell is derived from a G-CSF receptor.

Claim 43 (New): The method of claim 40, wherein said cell is a blood cell.

Claim 44 (New): A method for causing selective proliferation of a cell, said method comprising

(a) providing a cell including a vector that independently expresses

(i) a first gene that encodes a desired exogenous gene product; and

(ii) a second gene that encodes a chimeric protein comprising a first polypeptide and a second polypeptide, wherein said first polypeptide comprises a ligand binding domain of a steroid hormone receptor that, upon ligand binding, self-associates, and wherein said second polypeptide comprises a cytokine receptor or a part thereof that, upon said self-association of said first polypeptide, imparts proliferation activity to said cell; and

(b) exposing said cell to a ligand capable of binding to said ligand binding domain of said first polypeptide of said chimeric protein, thereby causing selective proliferation of said cell.

Claim 45 (New): The method of claim 44, wherein said steroid hormone receptor is an estrogen receptor.

Claim 46 (New): The method of claim 44, wherein said second polypeptide comprising a cytokine receptor or a part thereof that imparts proliferation activity to said cell is derived from a G-CSF receptor.

Claim 47 (New): The method of claim 44, wherein said cell is a blood cell.

REMARKS

Claims 7, 16, and 18-33 are pending in the present application. All claims stand finally rejected under 35 U.S.C. § 112, first and second paragraphs. Applicants address each of these rejections as follows.

Amendments

Claims 16 and 21-33 have been canceled and these canceled claims have been replaced with new claims 34-47. In addition, two translation errors in the specification have been corrected. No new matter has been added by these amendments.

Claim Objections

With regard to the present claim set, the Office states (page 2):

> A claim, which depends from a dependent claim, should not be separated by any claim that does not also depend from said dependent claim. In the present case, claims 18-20, which depend from claim 7, are separated from said claim 7 by independent claim 16. It should be kept in mind that a dependent claim may refer to any preceding claim. In general, applicant's sequence will not be changed.

Claims 16 and 21-33 have been canceled and re-numbered as new claims 34-47. Applicants submit that this amendment overcomes the Office's objection to the claim sequence.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 7, 16, and 18-33 stand finally rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Office asserts (page 3):

> A review of the response filed 23 February 2004 fails to locate a teaching of where support for the new claims and new claim language is to be found in the original specification ... In the absence of a showing of where such material is supported by the originally filed application, said new materials is [sic] considered to constitute new matter.

As an initial matter, Applicants note that the February 23, 2004 amendment stated that support for the amended and new claims is found throughout the specification, for example, at page 3 (line 9), in Figures 1 and 2, and in Examples 1-6, such as at page 9 (lines 12-16) of the English language translation of the specification. Applicants now direct the Office's attention to particular passages of the specification that support the present claims.

Support for the general method for causing selective proliferation of any cell utilizing a chimeric gene as presently claimed is found in the English language specification of the specification as originally filed, for example, at page 2 (lines 2-4) ("It has thus been desired to establish a system that enables selective amplification of cells containing an introduced gene"), at page 2 (lines 23-26) ("The present invention seeks to overcome the problem of poor gene introduction efficiency by selectively amplifying *in vivo* or *ex vivo* hematopoietic stem cells into which a gene for treatment has been

introduced"), at page 4 (line 13) and page 5 (lines 1-3) ("More specifically, the present invention relates to: ... a method for selectively proliferating the cell of (6), which comprises exposing the cell of (6) to a ligand capable of acting on the 'ligand-binding domain' of the fusion protein of (1)"), at page 4 (line 13) and page 5 (lines 23-26) (More specifically, the present invention relates to: ... a method for selectively proliferating the cell of (15), which comprises exposing the cell of (15) to a ligand capable of acting on the 'ligand-binding domain' of the fusion protein encoded by the gene contained in the vector of (8)"), at page 7 (lines 13-15) ("[I]n the present invention, the cell into which the vector is introduced includes hematopoietic stem cells, lymphatic cells, and cells other than these blood cells"), and at page 35 (lines 5-12) ("The present invention has made it possible to selectively amplify a cell into which an exogenous gene has been introduced, in response to an external stimulus, thereby enabling effective gene therapy even when the introduction efficiency of the gene into the target cells is low. Furthermore, since the system for selectively amplifying cells of the present invention can be applied to various blood cells, the range of cells targeted in gene therapy has been widened").

Additional support for the particularly claimed embodiments is also found in the application as filed. With respect to claims 7 and 40 *et seq.* (prior claim 26 *et seq.*), specific support for a "chimeric gene" or "chimeric protein" (or "fusion protein" as it is sometimes referred to in the instant specification) as claimed, i.e., a chimeric protein including a first polypeptide and a second polypeptide, where the first polypeptide

includes a ligand binding domain of a steroid hormone receptor that, upon ligand binding, self-associates, and where the second polypeptide includes a cytokine receptor or a part thereof that, upon the self-association of the first polypeptide, imparts proliferation activity to the cell, is found throughout the specification as originally filed, for instance, in Example 1.

Specific support for a method for causing selective proliferation (also referred to as "amplification" in the specification) of a cell, including the steps of providing a cell with a chimeric protein, gene, or vector and exposing the cell to a ligand capable of binding to the ligand binding domain (e.g., a steroid hormone), thereby causing selective proliferation of said cell is found in the specification as originally filed, for example, in the first full paragraph at page 4 ("The present invention relates to ... a method for selectively proliferating the cell either *in vivo* or *ex vivo* by exposing the cell to a steroid hormone. Furthermore, when the vector contains an exogenous gene, the present invention relates to a method for selectively proliferating a cell into which the exogenous gene has been introduced").

With respect to claims 34 and 44 (prior claims 16 and 30), specific support for the inclusion of a desired exogenous gene in combination with the gene encoding the chimeric protein is found in the specification as originally filed, for example, at page 5 (lines 18-19) ("wherein the 'gene encoding a fusion protein' and the 'exogenous gene' are located on the same molecule"). With respect to claims 18, 35 (prior claim 21), 41 (prior

claim 27), and 45 (prior claim 31), specific support for the recitation that the steroid hormone receptor is an estrogen receptor is found in the specification, for example, at page 4 (lines 25-26). Support for the recitation that the cytokine receptor be derived from a G-CSF receptor, as required by claims 19, 36 (prior claim 22), 42 (prior claim 28), and 46 (prior claim 32), is found, for example, at page 5 (lines 12-13) of the specification. The recitation, in claims 20, 39 (prior claim 25), 43 (prior claim 29), and 47 (prior claim 33), that the cell is a blood cell is found in the specification, for example, at page 3 (lines 7-12) ("In particular, if such a system is established for hematopoietic stem cells, which are the origin of many blood cell such as red blood cells or white blood cells and which are considered to be the most preferable target cells for gene therapy, it would contribute significantly to the field of gene therapy"), and with respect to claims 37 and 38 (prior claims 23 and 24), specific support for the recitation that the exogenous gene and chimeric gene be located on the same or separate molecules is found, for example, at page 5 (lines 18-21) of the specification.

In light of the above, Applicants submit that their claims are supported by the application as originally filed and the rejection under 35 U.S.C. § 112, first paragraph, should therefore be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 7, 16, and 18-33 stand rejected under 35 U.S.C. § 112, second paragraph, based on the assertion that the claims fail "to set forth the subject matter which applicant(s) regard as their invention." In particular, the Office states (page 3, page 4):

> Evidence that claims fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found at page 2, last paragraph, bridging to page 3 of the specification: 'The objective of the invention is to provide a fundamental technique for gene therapy targeting hematopoietic stem cells.' This statement indicates that the invention is different from what is defined in the claim(s) because the claims are now drawn to a generic method of proliferating virtually any cell, be it bacterial, plant or animal in origin.

Applicants address this rejection as it relates to the present claims (7, 18-20, and 34-47).

As an initial matter, Applicants note that, as discussed above, the English language translation of the original specification contains two translation errors. In particular, in reference to the sentence cited by the Office, Applicants first note that the original Japanese specification contains words equivalent to "hematopoietic stem cells, and such", where the phrase ", and such" was inadvertently omitted from the translation. Further, the phrase "the objective of the present invention..." in the sentence cited by the Office should correctly have been translated as "an objective of the present invention...." In view of these translation errors, Applicants submit that the scope of the invention set forth in the original application encompasses cells other than hematopoietic stem cells.

Moreover, Applicants submit that the instant specification clearly conveys that the disclosed invention is not limited to a specific set of cells. In this regard, Applicants direct the Office's attention to the specification at page 7 (lines 13-15) where Applicants teach that cells into which a vector is introduced include "hematopoietic stem cells, lymphatic cells, and cells other than these blood cells" (emphasis added). The scope of the invention set forth in Applicants' specification therefore encompasses cells other than blood cells and does not differ from the scope of the present claims. Accordingly, for all the above reasons, the rejection under 35 U.S.C. § 112, second paragraph, should be reconsidered and withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance and this action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the final Office Action for two (2) months, to and including December 21, 2004, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 21 December 2004

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